Impact of stringent versus lenient cardiovascular risk factor control on the incidence of cardiotoxicity in high-risk breast cancer patients

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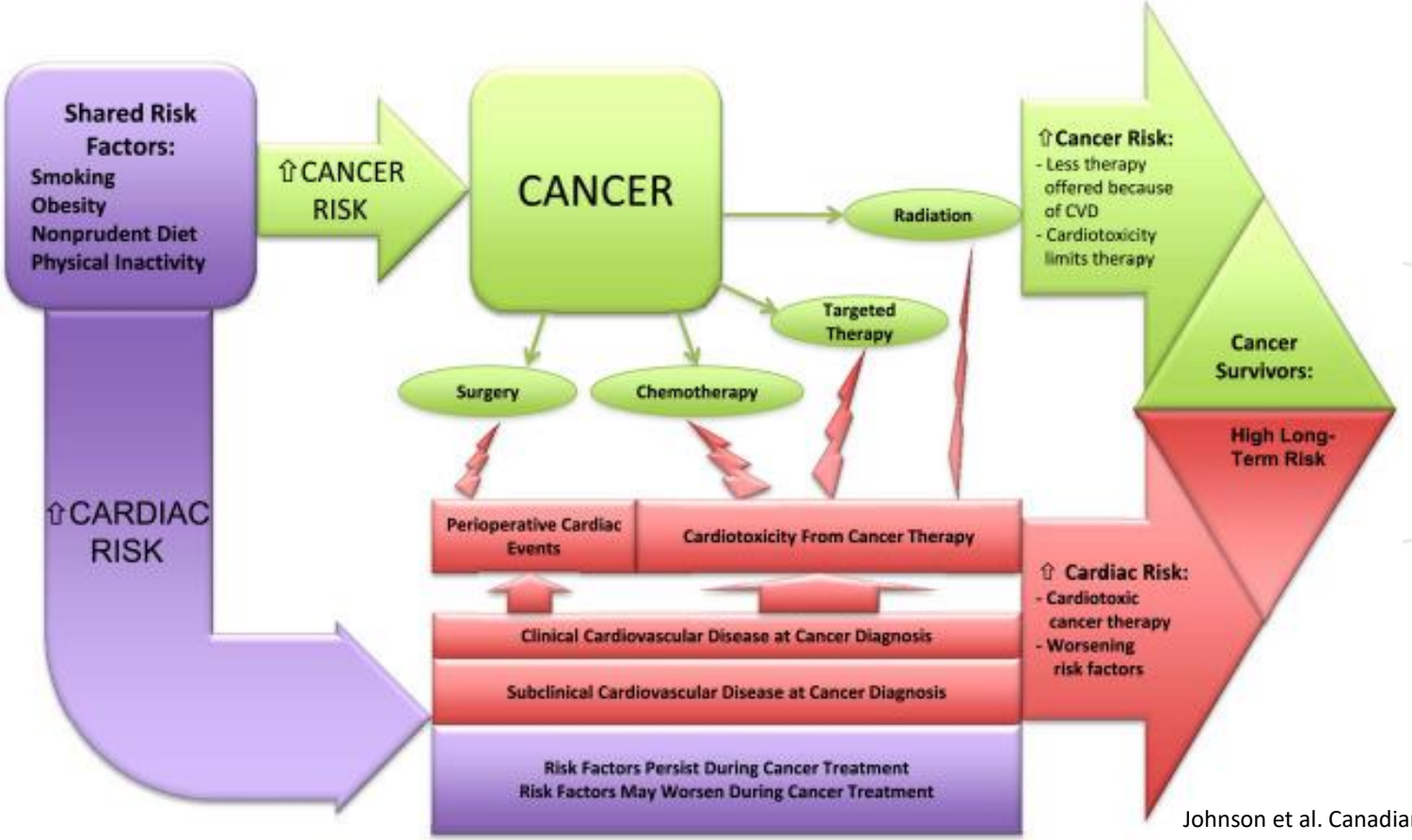
Introduction : common disease pathways



Johnson et al. Canadian J Cardiol 2016

Introduction : cardiotoxicity risk stratification

ESC European Society of Cardiology

European Journal of Heart Failure (2020) 22, 1945–1960
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POSITION PAPER

Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society

Table 2 Baseline cardiovascular risk stratification proforma for anthracycline chemotherapy

Risk factor	Score	Level of evidence	References
Previous cardiovascular disease			
Heart failure or cardiomyopathy	Very high	B	10,11
Severe valvular heart disease	High	C	11
Myocardial infarction or previous coronary revascularisation (PCI or CABG)	High	C	10–12
Stable angina	High	C	10–12
Baseline LVEF <50%	High	B	10
Borderline LVEF 50–54%	Medium[2]	C	
Cardiac biomarkers (where available)			
Elevated baseline troponin[a]	Medium[1]	C	13–15
Elevated baseline BNP or NT-proBNP[a]	Medium[1]	C	16,17
Demographic and cardiovascular risk factors			
Age ≥80 years	High	B	10,12,18
Age 65–79 years	Medium[2]	B	10,18–20
Hypertension[b]	Medium[1]	B	11,12,21
Diabetes mellitus[c]	Medium[1]	C	10–12
Chronic kidney disease[d]	Medium[1]	C	
Previous cardiotoxic cancer treatment			
Previous anthracycline exposure	High	B	18–20,22–25
Prior radiotherapy to left chest or mediastinum	High	C	20,22,23,26,27
Previous non-anthracycline-based chemotherapy	Medium[1]	C	24,25,28
Lifestyle risk factors			
Current smoker or significant smoking history	Medium[1]	C	23
Obesity (BMI > 30 kg/m^2)	Medium[1]	C	20,29,30
Risk level			

BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention.
Low risk = no risk factor OR one medium[1] risk factor; Medium risk = medium risk factors with a total of 2–4 points; High risk = medium risk factors with a total of ≥5 points OR any high risk factor; Very high risk = any very high risk factor.
[a]Elevated above the upper limit of normal for local laboratory reference range.
[b]Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or on treatment.
[c]Glycated haemoglobin >7.0% or >53 mmol/mol, or on treatment.
[d]Estimated glomerular filtration rate <60 mL/min/1.73 m^2.
Please see online supplementary *Table S2* for the 1 page printable version for clinical use.

Lyon et al. Eur J Heart Fail 2020

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Lyon et al. Eur J Heart Fail 2020

Table 3 Baseline cardiovascular risk stratification proforma for HER2-targeted cancer therapies (trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib)

Risk factor	Score	Level of evidence	References
Previous cardiovascular disease			
Heart failure or cardiomyopathy	Very high	C	31
Myocardial infarction or CABG	High	B	31,32
Stable angina	High	B	31–34
Severe valvular heart disease	High	C	31
Baseline LVEF <50%	High	C	
Borderline LVEF 50–54%	Medium[2]	B	35–37
Arrhythmia[a]	Medium[2]	C	31,32
Cardiac biomarkers (where available)			
Elevated baseline troponin[b]	Medium[2]	B	38,39
Elevated baseline BNP or NT-proBNP[b]	Medium[2]	C	17
Demographic and cardiovascular risk factors			
Age ≥80 years	High	B	32,33
Age 65–79 years	Medium[2]	B	35,36,40,41
Hypertension[c]	Medium[1]	B	32–36,42,43
Diabetes mellitus[d]	Medium[1]	C	31,32,42
Chronic kidney disease[e]	Medium[1]	C	32
Current cancer treatment regimen			
Includes anthracycline before HER2-targeted therapy	Medium[1f]	B	32,40,41,43–45
Previous cardiotoxic cancer treatment			
Prior trastuzumab cardiotoxicity	Very high	C	
Prior (remote) anthracycline exposure[g]	Medium[2]	B	42
Prior radiotherapy to left chest or mediastinum	Medium[2]	C	41,46,47
Lifestyle risk factors			
Current smoker or significant smoking history	Medium[1]	C	34
Obesity (BMI >30 kg/m^2)	Medium[1]	C	29,34,43,45
Risk level			

BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic

Introduction : cardioprotective strategies?

Year, Citation (Trial Name)	Cancer Therapy; Primary End Point	N	Medication	Follow-Up Period	Results	Conclusion
2006, Cardinale et al[7]	Anthracycline; LVEF decreased by 10%	114	Enalapril	12 mo	0 vs 43%; $P<0.001$	Benefit
2016, Gulati[8] (PRADA)	Anthracycline with or without trastuzumab; change in LVEF by cMRI	130	Candesartan	10–61 wk	Modest decline in LVEF with candesartan vs placebo ($P=0.025$)	Mild benefit with candesartan
			Metoprolol	10–61 wk	No change in LVEF with metoprolol vs placebo (P=NS)	No benefit
2016, Boekhout et al[9]	Trastuzumab; change in LVEF	206	Candesartan	2 mo	Candesartan had higher incidence of cardiac events vs placebo (P=NS)	No benefit, possible harm
2017, Pituskin et al[10] (MANTICORE 101-Breast)	Trastuzumab (25% with anthracyclines); reduce LV remodeling	94	Perindopril	52 wk	Attenuated LVEF decline but did not prevent LV remodeling	Possible benefit
			Bisoprolol	52 wk	Attenuated LVEF decline prevent LV remodeling	Possible benefit
2019, Guglin et al[11]	Trastuzumab only; LVEF decline and treatment interruptions	468	Lisinopril	1÷2 y follow-up	No difference from placebo	No benefit
			Carvedilol	1÷2 y follow-up	No difference from placebo	No benefit
	Trastuzumab plus anthracyclines; LVEF decline and treatment interruptions		Lisinopril	1÷2 y follow-up	HR: 0.53; $P=0.015$	Benefit
			Carvedilol	1÷2 y follow-up	HR: 0.49; $P=0.009$	Benefit

Brown et al. J Am Heart Assoc 2020

Introduction : cardioprotective strategies?

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			Metoprolol	10–61 wk	No change in LVEF with metoprolol …cebo (P=NS)	No benefit
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2019, Guglin et al[11]	Trastuzumab only; LVEF decline and treatment interruptions	468	Lisinopril	1+2 y follow-up	No difference from placebo	No benefit
			Carvedilol	1+2 y follow-up	No difference from placebo	No benefit
	Trastuzumab plus anthracyclines; LVEF decline and treatment interruptions		Lisinopril	1+2 y follow-up	HR: 0.53; $P=0.015$	Benefit
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Small trials
Low-risk patients
Short follow-up
Different treatments
Different endpoints

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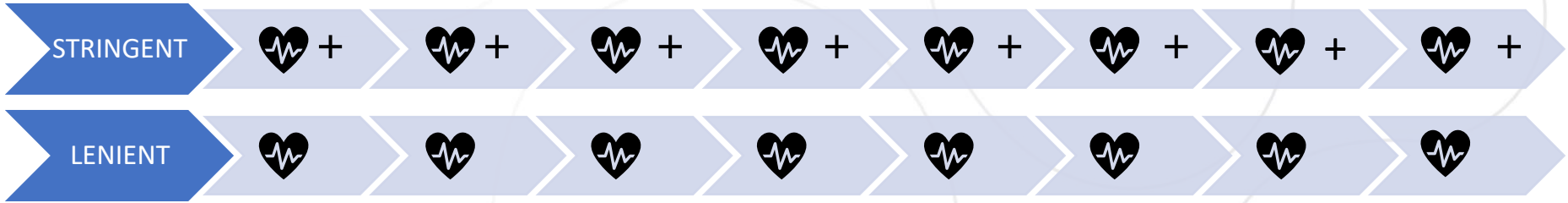
Study outline

New breast cancer diagnosis → **Cardio-onco referral for baseline evaluation** → **High** cardiotoxicity risk? → Evaluate inclusion eligibility

STUDY ENROLMENT & RANDOMIZATION



+ = ECG + TTE + lab + treat AHT, DM, dyslipidaemia, tobacco counseling

= ECG + TTE + lab

New cardiac abnormalities : further workup (at discretion of treating cardiologist)

Study outline : endpoints

→ Stringent CVRF management arm : Standard LVEF & GLS follow-up **+**

- office **BP target** <140/90mmHg (<130/80mmHg if <75y)
- **LDL cholesterol target** <115mg/dL (I° prev non-DM)
  <70mg/dL (I° prev. DM)
  <55mg/dL (II° prev.)
- **HbA1c target** <6,5% (<7,0% if >70y)
- **Smoking cessation** counseling

→ Lenient CVRF management arm (‘standard of care’ / ‘control’) :

- Standard LVEF & GLS follow-up

Study outline : endpoints

1. Impact of stringent vs. lenient control of CVRF in breast cancer patients with (very) high cardiotoxicity risk on oncological **treatment completion** and **progression-free survival**.
   → Role of laterality? Role of menopausal status?

2. Impact of stringent vs. lenient control of CVRF in breast cancer patients with (very) high cardiotoxicity risk on incidence of new cardiovascular events :
   - New-onset **cardiotoxicity** : clinical HF, subclinical LV systolic dysfunction
   - Major **adverse cardiovascular events** : CV death, AMI/ACS, stroke, systemic embolism, new arrhythmia, HF hospitalisation

3. **Validation** of pre-treatment risk stratification proformas in a real-life population undergoing breast cancer therapy.

Inclusion & exclusion criteria

Sample size : n = 528 (2x264)

INCLUSION	EXCLUSION
- Age ≥18y - **New breast cancer diagnosis**, scheduled for systemic therapy (anthracyclin-based and/or anti-HER2-based) - Pre-treatment cardiotoxicity risk stratification : **high / very high** - Written informed consent for study participation including repeat ECG & 2D TTE - Written informed consent for data collection & publication	- Age <18y - Pregnancy - Patient **not scheduled for systemic therapy** - **Pre-existing cardiovascular disease** (prior MI/PCI/CABG, CIED, LVEF <50%) - Unwilling / unable to provide informed consent - Enrolment in another clinical study potentially interfering with data collection

Additional value of this study ?

- ✓ Target population of high-risk patients

- ✓ Cumulative effect of global cardiovascular risk profile optimization > 1 intervention?
- ✓ Endpoints involve both oncology & cardiology outcomes

- ✓ Standardized short-term cardio-oncology follow-up in both arms (q3m)
- ✓ Standardized long-term cardio-oncology follow-up in both arms (q6m)

Thank you for your attention

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Follow-up : short term

First 2 years after enrolment (= first 2 years on-treatment)

→ Cardio-oncology evaluation q3m (both arms)
= ECG + TTE + lab + clinical evaluation

→ Stringent CVRF management arm : Standard LVEF & GLS follow-up **+**
- office **BP target** <140/90mmHg (<130/80mmHg if <75y)
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- **HbA1c target** <6,5% (<7,0% if >70y)
- **Smoking cessation** counseling

→ Lenient CVRF management arm (‘standard of care’ / ‘control’) :
- Standard LVEF & GLS follow-up

Follow-up : long term

>2 years after enrolment

→ Cardio-oncology evaluation **q6m** (both arms)
= ECG + TTE + lab + clinical evaluation

→ Stringent CVRF management arm : Standard LVEF & GLS follow-up **+**
- office **BP target** <140/90mmHg (<130/80mmHg if <75y)
- **LDL cholesterol target** <115mg/dL (I° prev non-DM)
<70mg/dL (I° prev. DM)
<55mg/dL (II° prev.)
- **HbA1c target** <6,5% (<7,0% if >70y)
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→ Lenient CVRF management arm (‘standard of care’ / ‘control’) :
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